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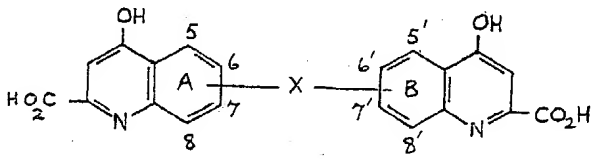
(54) QUINOLINE DERIVATIVES

(71) We, IMPERIAL CHEMICAL INDUSTRIES LIMITED, of Imperial Chemical House, Millbank, London, S.W.1., a British Company, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new quinoline derivatives, and more particularly it relates to new bis-kynurenic acid derivatives which are active as inhibitors of the effects following the combination of reagin-like antibodies and their antgens. They are therefore useful for the treatment of asthma, for example allergic asthma, and for the treatment of other syndromes or diseases initiated by an antigen-antibody reaction, for example hay fever, urticaria and auto-immune diseases.

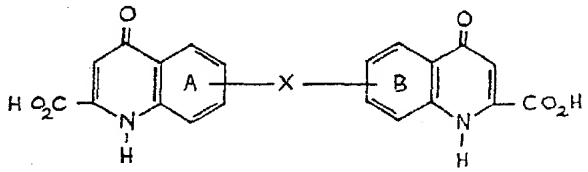
According to the invention there are provided bis-kynurenic acids of the formula:—



I

wherein either or both of the benzene rings A and B optionally bear a methyl radical or not more than two halogen atoms, and X is linked to positions 6,6' or 8,8' of rings A and B, and X stands for a covalent bond (i.e. a direct link between rings A and B) or $-(CH_2)_2-$, $-(CH_2)_3-$, $-O(CH_2)_2O-$, $-O(CH_2)_2O-$, —O—, —S—, —NH—, —N=N— or —CONH—, and non-toxic pharmaceutically-acceptable salts thereof, but excluding 2,2'-dicarboxy-4,4'-dihydroxy-8,8'-biquinolyl or a non-toxic pharmaceutically-acceptable salt thereof.

It is to be understood that the compounds of the formula I can exist in the tautomeric form of the formula:—



II

wherein A, B and X have the meanings stated above. However, for convenience the compounds will all be referred to as quinoline derivatives in this specification.

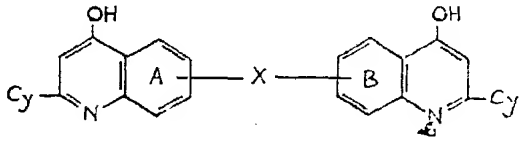
As one particular embodiment of this invention there may be mentioned, for example, compounds of the formula I wherein rings A and B are identical.

The optional halogeno substituent(s) in ring A or B may be selected from fluorine, chlorine and bromine atoms.

Suitable salts of the invention are salts containing a non-toxic pharmaceutically-acceptable cationic moiety, for example ammonium, alkali metal, alkaline earth metal or aluminium salts or salts with non-toxic pharmaceutically-acceptable organic bases, for example piperidine, triethanolamine or ethylenediamine.

Preferred compounds of this invention are 1,2-bis(2-carboxy-4-hydroxyquinol-6-yl)ethane, 2,2′-dicarboxy-8,8′-dimethyl-4,4′-dihydroxy-6,6′-biquinolyl and 2,2′-dicarboxy-8,8′-dichloro-4,4′-dihydroxy-6,6′-biquinolyl, and non-toxic pharmaceutically-acceptable salts thereof.

According to a further feature of the invention there is provided a process for the manufacture of the bis-kynurenic acids of the formula I, which comprises hydrolysing a compound of the formula: —



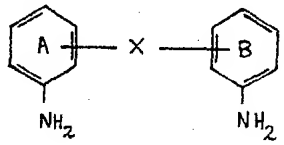
III

wherein A, B and X have the meanings stated above, and Cy stands for a C_{2-7} alkoxycarbonyl, C_{8-11} phenylalkoxycarbonyl, phenoxycarbonyl, cyano or carbamoyl (—$CONH_2$) radical.

The hydrolysis is carried out in the presence of water, and an organic solvent may optionally be present. As a suitable hydrolytic agent there may be mentioned, for example, an alkali metal hydroxide, for example sodium hydroxide or potassium hydroxide, or an inorganic acid, for example sulphuric or hydrochloric acid. The hydrolysis is conveniently carried out at a moderately elevated temperature, for example a temperature of 50—150°C., for example reflux temperature.

The salts of the invention are obtainable from carboxylic acid derivatives of the formula I by standard methods.

Those of the starting materials of the formula III wherein Cy stands for a C_{2-7} alkoxycarbonyl, C_{8-11} phenylalkoxycarbonyl or phenoxycarbonyl radical may be obtained by the Conrad-Limpach reaction. The first stage of this reaction comprises reacting a diamino compound of the formula: —

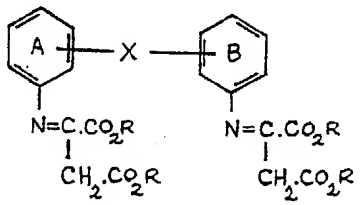


IV

wherein A, B and X have the meanings stated above, with a compound of the formula: —

$RO_2C . CH_2 . CO . CO_2R$ V

wherein R stands for a C_{1-6} alkyl, C_{7-10} phenylalkyl or phenyl radical, at a moderately elevated temperature, for example 80—110°C., in an aromatic hydrocarbon solvent, for example benzene, in an apparatus which facilitates the removal of water from the reaction mixture, for example a Dean and Stark apparatus. This gives a compound which in one of its tautomeric forms has the formula: —



VI

wherein A, B, R and X have the meanings stated above.

The second stage of the reaction involves ring-closing a compound of the formula VI by heating it at 230—250°C., for example in diphenyl ether or α-chloronaphthalene.

Alternatively, an essentially similar procedure can be used, but using the appropriate ester of acetylene dicarboxylic acid in place of the ester of the formula V.

The amides and nitriles of the formula III may be obtained from the corresponding esters by standard methods.

The activity of the compounds of this invention is demonstrated by their ability to inhibit in the rat passive cutaneous anaphylaxis, induced by reaginic antibodies to egg albumin using *B. pertussis* as an adjuvant. When the said compounds are used to treat asthma in man by inhalation, a typical dose is from 0.01 mg. to 1 mg/kg. at suitable intervals when relief or prevention of allergic airway obstruction is required. When they are used intravenously to treat asthma in man, a typical total daily dose is 25 mg. per man. When they are used in man to treat other syndromes or diseases initiated by an antigen-antibody reaction, and being administered by inhalation or intravenously, a typical total daily dose is 25 mg. per man.

According to a further feature of the invention there are provided pharmaceutical compositions comprising a compound of the formula I, wherein A, B and X have the meanings stated above, or a non-toxic pharmaceutically-acceptable salt thereof, but excluding 2,2′-dicarboxy-4,4′-dihydroxy-8,8′-biquinolyl or a non-toxic pharmaceutically-acceptable salt thereof, and an inert non-toxic pharmaceutically-acceptable diluent or carrier.

The said pharmaceutical compositions are obtainable by well known methods using conventional diluents or carrier. The compounds of formula I are useful for the treatment of allergic asthma, and for this purpose the said compositions may be in a form suitable for administration by inhalation. Suitable compositions comprise a mixture of the active ingredient with a solid diluent or carrier, for example lactose, the said mixture being in fine particulate form suitable for administration from a powder inhalation device. Alternatively, the compositions may be administered by inhalation in the form of a suspension or solution in a suitable liquid, for example water or an aqueous or non-aqueous medium, using a conventional nebulizer or a pressurised container.

Alternatively, the pharmaceutical compositions of the invention may be in a form suitable for intravenous administration.

The pharmaceutical compositions of the invention may also contain, in addition to a compound of the formula I or a non-toxic pharmaceutically-acceptable salt thereof one or more known active ingredients selected from β-adrenergic stimulants, for example isoprenaline, adrenaline, orciprenaline, isoethacine, and pharmaceutically-acceptable acid-addition salts thereof, for example a sulphate, and prostaglandins having bronchodilatory activity, for example prostaglandin E_1 or E_2, and phosphodiesterase inhibitors selected from the following compounds: —

(a) 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine;

(b) 2 - amino - 4,6 - di - C_{1-4} - alkyl - 5 - oxo - 4,5 - dihydro - s - triazolo[1,5-

a]pyrimidines, for example 2-amino-6-methyl-5-oxo-4-n-propyl-4,5-dihydro-s-triazolo[1,5-a]pyrimidine;

(c) theophylline and related 3,5-di-C_{1-4}-alkylxanthines; and

(d) 6,8 - di - C_{1-4} - alkyl - 5,6 - dihydro - 5 - oxo - s - triazolo[4,3 - c]pyrimidines, for example 5,6-dihydro-5-oxo-6,8-di-n-propyl-s-triazolo[4,3-c]pyrimidine.

The pharmaceutical compositions of this invention may contain from 1% to 50% by weight of a compound of the formula I or a non-toxic pharmaceutically-acceptable salt thereof.

The invention is illustrated by the following non-limiting Examples:—

Example 1

1,2-Bis-(2-ethoxycarbonyl-4-hydroxyquinol-6-yl)ethane (1 g.) was heated with 10% w/v aqueous sodium hydroxide (10 ml.) on a steam bath for 30 minutes, and the hot solution was then acidified with 10N-hydrochloric acid (3 ml.). The resultant precipitate was collected by filtration, dissolved as much as possible in saturated sodium hydrogen carbonate solution (50 ml.), the mixture filtered, and the filtrate acidified with 10N-hydrochloric acid (6 ml.). The resultant precipitate was collected by filtration and washed successively with water and hot ethanol. There was thus obtained 1,2-bis-(2-carboxy-4-hydroxyquinol-6-yl)ethane monohydrate, m.p. 296°C. (decomposition).

The ester used as starting material was obtained as follows:—

Sodio diethyl oxalacetate (15.8 g.) was added portionwise to a stirred mixture of 10N-hydrochloric acid (10 ml.), water (100 ml.) and benzene (50 ml.) at a temperature not exceeding 20°C. The mixture was stirred for 1 hour and the benzene layer was then separated and washed with water (50 ml.). The aqueous washings were back-extracted with benzene (50 ml.) and the combined benzene solutions were dried over anhydrous magnesium sulphate and filtered. 4,4'-Diaminodibenzyl (4.2 g.) was added and the mixture was boiled in an apparatus for continuously removing water from the reaction mixture (a Dean and Stark apparatus) until no more water was collected. The benzene was removed *in vacuo* and the residue was added over 5 minutes to boiling diphenyl ether (50 ml.). The mixture was heated at 220—240°C. until no more ethanol was liberated (about 3 minutes). The solution was cooled to room temperature and diluted by the addition of petroleum ether (b.p. 40—60°C; 500 ml.). After standing for 30 minutes, the suspension was filtered and the solid residue washed several times with petroleum ether (b.p. 40—60°C.). There was thus obtained, as solid residue, 1,2-bis-(2-ethoxycarbonyl-4-hydroxyquinol-6-yl)ethane, m.p. 314—316°C. (decomposition) (crystallised from dimethylsulphoxide and washed several times with boiling ethanol).

Example 2

The method described in Example 1 was repeated using the appropriate diamino derivative as starting material, and the following compounds were obtained:—

bis-(2-carboxy-4-hydroxyquinol-6-yl)ether, m.p. 270°C. (decomposition) from 4,4'-diaminodiphenyl ether;

2,2'-dicarboxy-8,8'-dimethyl-4,4'-dihydroxy-6,6'-biquinolyl monohydrate, m.p. 290°C. (decomposition) from 4,4'-diamino-3,3'-dimethyldiphenyl;

2,2'-dicarboxy-8,8'-dichloro-4,4'-dihydroxy-6,6'-biquinolyl, m.p. over 360°C., from 4,4'-diamino-3,3'-dichlorodiphenyl;

1 - (2 - carboxy - 5,7 - dichloro - 4 - hydroxyquinol - 6 - yloxy) - 2 - (2 - carboxy-4 - hydroxyquinol - 6 - yloxy)ethane monohydrate, m.p. 250°C. (decomposition) from 1-(4-amino-2,6-dichlorophenoxy)-2-(4-aminophenoxy)ethane (see below for details on preparation);

1,2-bis-(2-carboxy-4-hydroxyquinol-8-yloxy)ethane monohydrate, m.p. 280°C. (decomposition) from 1,2-bis(2-aminophenoxy)ethane;

2,2'-dicarboxy-4,4'-dihydroxy-6,6'-azoquinoline, m.p. 305—307°C. (decomposition) from 4,4'-diaminoazobenzene; and

bis-(2-carboxy-4-hydroxyquinol-6-yl)amine, m.p. 340—346°C. (decomposition) (crystallising with one molecule of dimethylsulphoxide from dimethylsulphoxide and water) from 4,4'-diaminodiphenylamine.

The 1-(4-amino-2,6-dichlorophenoxy)-2-(4-aminophenoxy)ethane used as starting material for the preparation of 1-(2-carboxy-5,7-dichloro-4-hydroxyquinol-6-yloxy)-2-(2-carboxy-4-hydroxyquinol-6-yloxy)ethane was obtained as follows:—

An intimate mixture of 4-acetamido-2,6-dichlorophenol (16.5 g.; m.p. 168—

169°C.), anhydrous potassium carbonate (10.4 g.) and 1-(4-acetamidophenoxy)-2-bromoethane (19.35 g.) was heated at 150—160°C. for 12 hours. The mixture was cooled and the solid residue boiled with water (200 ml.) and filtered. The solid residue was dissolved in 2-ethoxyethanol (200 ml.), treated with charcoal and filtered hot. The filtrate was poured into water (200 ml.) and made alkaline with 5N-sodium hydroxide. The resulting mixture was filtered, and the solid residue was washed with water and dried at 60°C. The solid (m.p. 182—184°C.) was boiled with ethanol (250 ml.) for 30 minutes, and then cooled and filtered. The solid residue (mp. 206—208°C.) was crystallised from a mixture of glacial acetic acid and water (3:1), and there was thus obtained 1-(4-acetamido-2,6-dichlorophenoxy)-2-(4-acetamidophenoxy)-ethane, m.p. 206—208°C.

A mixture of this acetyl derivative (25 g.), ethanol (150 ml.) and concentrated hydrochloric acid (150 ml.) was heated under reflux on a steam bath for 6 hours. The mixture was then cooled and filtered, and the solid residue was dissolved in hot water (350 ml.), treated with charcoal, filtered, and acidified with concentrated hydrochloric acid (100 ml.). The mixture was cooled and filtered, and the solid residue was dissolved in hot water (300 ml.) and filtered. Ethanol (150 ml.) was added to the filtrate, the hot solution was treated with charcoal and filtered, and the filtrate was acidified with concentrated hydrochloric acid (100 ml.). The mixture was cooled and filtered, and the solid residue was dried at 60°C. There was thus obtained 1-(4-amino-2,6-dichlorophenoxy)-2-(4-aminophenoxy)ethane dihydrochloride, m.p. above 280°C. (darkened at 240—250°C.).

Example 3

The method described in Example 1 was repeated using the appropriate diamino derivative as starting material, and the following compounds were obtained:—

1,3-bis(2-carboxy-4-hydroxyquinol-6-yloxy)propane, m.p. 260°C. (decomposition) (crystallised from dimethylsulphoxide/ethanol) from 1,3-bis(4-aminophenoxy)-propane; and

bis(2-carboxy-4-hydroxyquinol-6-yl)sulphide dihydrate, m.p. 280—290°C. (decomposition) from 4,4′-diaminodiphenyl sulphide.

Example 4

4 - Hydroxy - 6 - (4 - hydroxy - 2 - methoxycarbonylquinol - 6 - ylcarbamoyl)-2 - methoxycarbonylquinoline (1.6 g.) was heated with 2N-sodium hydroxide (20 ml.) on a steam bath for 30 minutes. The solution was filtered and the filtrate acidified with concentrated hydrochloric acid. The resulting mixture was filtered and the solid residue washed successively with water and hot dimethylsulphoxide. The solid residue (which did not melt below 360°C.) was 2-carboxy-6-(2-carboxy-4-hydroxyquinol-6-ylcarbamoyl)-4-hydroxyquinoline, n.m.r. spectrum (in NaOD): H_2, H_3, single peak (6.95 δ); H_5, double peak (8.85 δ); H_6, $H_{7'}$, H_8, $H_{7'}$, H_8, multiple peaks (7.80—8.30 δ).

The ester used as starting material was prepared as follows:—

A solution of acetylene dicarboxylic acid dimethyl ester (5.7 g.) in dry methanol (25 ml.) was added to a solution of *N*-(4-aminobenzoyl)-*p*-phenylenediamine (4.5 g.) in dry methanol (100 ml.). When the initial exothermic reaction was over, the mixture was heated under reflux for 4 hours. The methanol was removed by distillation under reduced pressure, and the residue was dissolved in chloroform (200 ml.), and washed successively with water (2×100 ml.), N-hydrochloric acid (2×100 ml.), N-sodium hydroxide (2×200 ml.) and water (2×100 ml.). The chloroform solution was dried over anhydrous magnesium sulphate, filtered and the solvent removed by distillation. A sample of the solid residue (m.p. 188—194°C.) was crystallised from methyl acetate, and had m.p. 192—194°C. The crude solid (4 g.) was added to boiling diphenyl ether (150 ml.), and the mixture kept at 220—240°C until no more methanol was liberated (about 15 minutes). The solution was cooled and filtered, and the solid residue (m.p. 344—348°C.) was washed with acetone and crystallised from dimethylsulphoxide. There was thus obtained 4 - hydroxy - 6 - (4-hydroxy - 2 - methoxycarbonylquinol - 6 - ylcarbamoyl) - 2 - methoxycarbonylquinoline, m.p. 348—350°C. (decomposition).

Example 5

A solution of 2,2′-diethoxycarbonyl-8,8′-dichloro-4,4′-dihydroxy-6,6′-biquinolyl (0.3 g.) in a mixture of hot glacial acetic acid (40 ml.) and 3N-hydrochloric acid (10 ml.) was heated under reflux for 10 hours. The mixture was cooled and filtered, and

the solid residue was washed successively with water, methanol and ether. The solid residue was crystallised from dimethylsulphoxide and washed with hot ethanol. There was thus obtained 2,2′-dicarboxy-8,8′-dichloro-4,4′-dihydroxy-6,6′-biquinolyl (m.p. above 360°C.); n.m.r. spectrum (in NaOD): H_3 single peak (7.00 δ); H_5 double peak (8.45 δ); H_7 double peak (8.15 δ).

The ester used in the above process was obtained by the method described in Example 1 using an equivalent weight of 4,4′-diamino-3,3′-dichlorodiphenyl as starting material in place of 4,4′-diaminodibenzyl, and using an equivalent weight of α-chloronaphthalene in place of diphenyl ether as solvent in the cyclisation process. The ester had m.p. 288—290°C. (decomposition) (crystallised from dimethylsulphoxide and washed with boiling ethanol).

Example 6

2,2′-Dicarboxy-8,8′-dimethyl-4,4′-dihydroxy-6,6′-biquinolyl monohydrate (0.4 g.) was stirred with a solution of sodium hydrogen carbonate (0.17 g.) in water (10 ml.) for one hour. The mixture was filtered, the filtrate diluted with ethanol (12 ml.), and the resulting mixture filtered. The solid residue was washed successively with ethanol and ether, and then dried. There was thus obtained the disodium salt of 2,2′-dicarboxy-8,8′-dimethyl-4,4′-dihydroxy-6,6′-biquinolyl.

Example 7

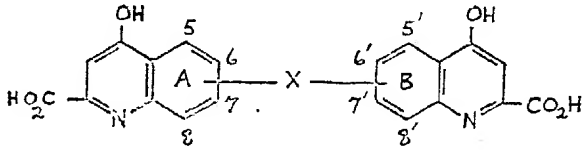
An aerosol formulation was prepared consisting of finely divided disodium salt of 2,2′-dicarboxy-8,8′-dimethyl-4,4′-dihydroxy-6,6′-biquinolyl, 2% w/w (screened through mesh size 90; British Standard 410: 1962) isoprenaline sulphate 0.1% w/w (screened through mesh size 90), and propellant to 100% w/w (the propellant was a 60:40 v/v mixture of dichloro-difluoromethane and 1,2-dichloro-1,1,2,2-tetrafluoroethane).

Example 8

2,2′-Dicarboxy-8,8′-dichloro-4,4′-dihydroxy-6,6′-biquinolyl (20 g.; screened through mesh size 90), isoprenaline sulphate (0.1 g.; screened through mesh size 90) and lactose (15 g.; screened through mesh size 90) were thoroughly mixed. There was thus obtained a powder formulation suitable for inhalation for medicinal purposes.

WHAT WE CLAIM IS:—

1. A bis-kynurenic acid of the formula:—



I

wherein either or both of the benzene rings A and B may optionally bear a methyl radical or not more than two halogen atoms, and X is linked to positions 6,6′ or 8,8′- of rings A and B, and X stands for a covalent bond or $-(CH_2)_2-$, $-(CH_2)_3-$, $-O(CH_2)_2O-$, $-O(CH_2)_3O-$, $-O-$, $-S-$, $-NH-$, $-N=N-$ or $-CONH-$, or a non-toxic pharmaceutically-acceptable salt thereof, but excluding 2,2′-dicarboxy-4,4′-dihydroxy-8,8′-bisquinolyl or a non-toxic pharmaceutically-acceptable salt thereof.

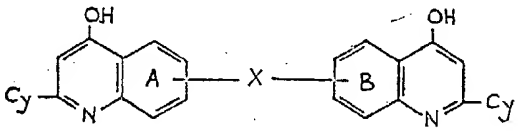
2. A compound as claimed in claim 1 wherein rings A and B are identical.

3. A compound as claimed in claim 1 or 2 wherein the optional halogeno substituent(s) in ring A or B is or are selected from fluorine, chlorine and bromine atoms.

4. A salt as claimed in any of claims 1 to 3 which is an ammonium, alkali metal, alkaline earth metal or aluminium salt or a salt with a non-toxic pharmaceutically-acceptable organic base.

5. A compound as claimed in claim 1, 2 or 3 which is 1,2-bis-(2-carboxy-4-hydroxyquinol-6-yl)ethane, 2,2′-dicarboxy-8,8′-dimethyl-4,4′-dihydroxy-6,6′-biquinolyl or 2,2′-dicarboxy-8,8′-dichloro-4,4′-dihydroxy-6,6′-biquinolyl, or a non-toxic pharmaceutically-acceptable salt thereof.

6. A process for the manufacture of a bis-kynurenic acid derivative claimed in claim 1, which comprises hydrolysing a compound of the formula: —



III

wherein A, B and X have the meanings stated in claim 1, and Cy stands for a C_{2-7} alkoxycarbonyl, C_{8-11} phenylalkoxycarbonyl, phenoxycarbonyl, cyano or carbamoyl radical.

7. A process as claimed in claim 6 in which the hydrolytic agent is an alkali metal hydroxide or an inorganic acid.

8. A pharmaceutical composition comprising a compound of the formula I, wherein A, B and X have the meanings stated in claim 1, or a non-toxic pharmaceutically-acceptable salt thereof, but excluding 2,2′-dicarboxy-4,4′-dihydroxy-8,8′-biquinolyl or a non-toxic pharmaceutically-acceptable salt thereof, and an inert non-toxic pharmaceutically-acceptable diluent or carrier.

9. A composition as claimed in claim 8 which is in a form suitable for administration by inhalation.

10. A composition as claimed in claim 8 which is in a form suitable for intravenous administration.

11. A composition as claimed in any of claims 8 to 10 which contains, in addition to a compound of the formula I or a non-toxic pharmaceutically-acceptable salt thereof, one or more known active ingredients selected from β-adrenergic stimulants, prostaglandins having bronchodilatory activity, and phosphodiesterase inhibitors selected from the following compounds: —

(a) 3-acetamido-6-methyl-8-n-propyl-s-triazolo[4,3-a]pyrazine;
(b) 2-amino-4,6-di-C_{1-4}-alkyl-5-oxo-4,5-dihydro-s-triazolo[1,5-a]pyrimidines;
(c) theophylline and related 3,5-di-C_{1-4}-alkylxanthines; and
(d) 6,8-di-C_{1-4}-alkyl-5,6-dihydro-5-oxo-s-triazolo[4,3-c]pyrimidines.

12. A composition as claimed in any of claims 8 to 11 which contains 1% to 50% by weight of a compound of the formula I or a non-toxic pharmaceutically-acceptable salt thereof.

13. A compound of the formula I, wherein A, B and X have the meanings stated in claim 1, or a non-toxic pharmaceutically-acceptable salt thereof, whenever prepared by a process claimed in claim 6 or 7.

14. A compound as claimed in claim 1, substantially as described in Example 1 or 2.

15. A compound as claimed in claim 1 substantially as described in any of Examples 3 to 6.

16. A pharmaceutical composition as claimed in claim 8, substantially as described in Example 7 or 8.

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